Remarks

Amendment of the Claims

Claim 7 has been amended to further clarify that the engagement between the disruption element and the inner surface of the container consists essentially of rolling contact. Support for this amendment is found at paragraph [0008] of the published application. The claim has also been amended to make clear that the process is used to disrupt human cells and tissues as is evidenced in the entirety of the specification. Thus, no new matter has been added.

Obviousness Rejections

Claims 7, 8, and 16 have been rejected as obvious over Spelsberg in view of Emanuel, Murphy, Hoon, and Bassett. This rejection is respectfully traversed for the following reasons.

The Spelsberg reference is cited by the Examiner as showing the disruption of cells or tissues by an element in the presence of "a solution" using a disruption element that employs "a rotating-type rolling contact". Basset and Hoon are said to add to this by teaching that the solution could be a nucleic acid stabilizing solution. Emanuel is said to provide the impetus for conducting the tissue disruption process in 45 seconds or less. Murphy is said to provide the impetus for decanting step.

The claims of the instant indicates that the disruption occurs as a result of contact that consists essentially of rolling contact between the disruption element, the container wall, and the specimen (and thus not sonication or substantially vibrational motion). An element of the device such as a ball is rotated through the container such that the area of the element is at various times in and out of contact with the inner wall of the container. This is not true of the manner in which the Spelsberg device is fashioned and used.

While it is true that a sliding body in contact with another body can exhibit *some* rolling contact, the drawings and description of the Spelsberg device clearly shows that the

overwhelming majority of contact between the disruption element (pestle) and the container wall is sliding contact and that it is this effect that is relied upon for tissue disruption. The contact does not consist essentially of rolling contact as in the instant invention.

The Spelsberg device uses a pestle member as the disruption element. The pestle is pushed downward through the container and its entire cylindrical surface is in contact with the wall of the container throughout the entirety of its journey. A shaft is used to drive the pestle and impart a rotational movement to the pestle. No part of the surface of the pestle (other than any grooves that might be present) is ever out of contact with the container wall as the pestle is moved. This is the essence of sliding contact. Indeed, it does not seem feasible that one could even fashion an element such as a ball to function in the manner of the pestle of the Spelsberg device.

Spelsberg is further distinguished from the instant invention in the manner in which one collects worked sample. Spelsberg states, "The homogenized tissue solution empties into the second chamber portion from which it is discharged." Col. 2, line 48. Even the title indicates this as it is a "*Continuous Flow* Tissue Homogenizer" (emphasis added). Thus, unlike the claimed method of the instant invention, the Spelsberg device does not involve decanting supernatant from the worked sample. Rather, it involves passage of the worked sample through an opening and collection in a separate vessel.

Emanuel is directed to a device that employs a piston to squeeze tissues apart and then drains the extract through an orifice. In this described device too sliding contact is the predominant effect used to attain tissue disruption, not rolling contact. For example, Emanuel states that "One or more gaskets like o-ring 50 should be provided in recessed portions of piston 48 to insure a uniform contact between the piston 48 and the wall of chamber 14". Col. 2, lines 32-35. This type of arrangement does not lend itself to contact that consists essentially of rolling contact as in the case of the instant invention.

Emanuel is further distinguished from the instant invention by the manner in which worked solution is extracted. As Emanuel notes, "A piston which applies the pressure forces the suspension through a small annular orifice into a region of low pressure" and "the homogenate drains out through the vent passage 44 to the delivery tube." Col. 1, line 49 and col. 4, line 52. Indeed, the size of the orifice is critical to effect the ejection that is a feature of the use of the device. Col. 3, lines 1-5. Thus, unlike the claimed method of the instant invention, the Emanuel device also does not involve decanting supernatant from the worked sample. Rather, it involves ejection of the worked sample--a wholly different approach. Thus, even if one were to combine the Emanuel and Spelsberg devices they would have a disruption device that relies on sliding contact for effect and which operates to collect worked sample by ejection or drainage, not decantation.

The Bassett reference has been reviewed but applicants' attorney is unable to find any description of a tissue disruption process requiring the use of a nucleic acid -stabilizing solution as the Examiner has asserted. The cited portion of that patent (Col. 28, lines 50-67) describes freezing tumor samples in liquid nitrogen until RNA is extracted and no further elaboration is given. Thus, the Bassett patent should not be applied against the instant invention.

Hoon proposes the extraction of RNA "using Tri-Reagent according to the manufacturer's protocol (Molecular Research Center, Inc., Cincinnati, Ohio)." Col. 32, lines 32-36. The manufacturer's protocol as posted on the Internet by the manufacturer states that "The entire procedure can be completed in 1 h and the recovery of undegraded mRNAs is 30-150% greater than with other methods of RNA isolation." *See,* Molecular Research Center, Inc. site at http://www.mrcgene.com/tri.htm. Thus, following the teaching of Hoon would not lead one to a process in which tissue disruption occurred in 45 seconds or less as claimed in claim 7 nor would it be suggest that it would be well suited for the intraoperative procedure of claim 16 (and as described in the specification of the instant invention). Accordingly, Hoon does not suggest any aspect of the present

invention and is not combinable with the other references cited by the Examiner for such an application.

The Murphy patent is directed entirely to methods of releasing RNA and DNA from microorganisms that are difficult to "crack" such as the tuberculosis bacterium. This is distinguishable in itself from the human cell and tissue process of the instant invention. Further, because it is directed to use in the organisms described, the Murphy process relies on sonication or vibration to effect the disruption. These processes are vastly different from the piston-driven processes cited by the Examiner and thus make it unlikely that a skilled artisan would look to Murphy for enhancements or modifications to Spelsberg or Emanuel. Further, Murphy teaches that similar prior art methods that incorporate friction, as is the case in both Spelman and Emanuel, are not desirable. Col. 3, lines 50-57. This also very strongly and directly militates against combining these references.

The differences between the cited references and the claimed methods are significant. Furthermore, there is nothing to suggest the combination of the references in the manner presented and there are significant reasons why they should not be combined. Accordingly, the claimed invention is not obvious and a timely notice of allowance is respectfully solicited.

Respectfully submitted,
/Todd Volyn/
Todd F. Volyn
Reg. No. 37,463

Johnson & Johnson.
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
Telephone: 732-524-6202
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